



US009303054B2

(12) **United States Patent**
Lothschuetz et al.

(10) **Patent No.:** **US 9,303,054 B2**
(45) **Date of Patent:** **Apr. 5, 2016**

(54) **PROCESS FOR THE DIASTEREOSSELECTIVE PREPARATION OF RUTHENIUM COMPLEXES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/781,980**

(22) PCT Filed: **Apr. 1, 2014**

(86) PCT No.: **PCT/EP2014/056495**

§ 371 (c)(1),

(2) Date: **Oct. 2, 2015**

(87) PCT Pub. No.: **WO2014/166777**

PCT Pub. Date: **Oct. 16, 2014**

(65) **Prior Publication Data**

US 2016/0046658 A1 Feb. 18, 2016

(30) **Foreign Application Priority Data**

Apr. 8, 2013 (EP) 13162679

(51) **Int. Cl.**

C07F 15/00 (2006.01)

B01J 31/24 (2006.01)

(52) **U.S. Cl.**

CPC **C07F 15/0053** (2013.01); **B01J 31/2409**

(2013.01); **B01J 2231/643** (2013.01); **B01J**

2531/821 (2013.01)

(58) **Field of Classification Search**

USPC 546/10, 2

See application file for complete search history.

(56) **References Cited**

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Baratta et al, "2-(Aminomethyl)pyridine-Phosphine Ruthenium (II) Complexes: Novel Highly Active Transfer Hydrogenation Catalysts"; *Organometallics* 2005, 24:1660-1669.

Carpenter et al, "Convenient and improved protocols for the hydrogenation of esters using Ru catalysts derived from (P,P), (P,N,N) and (P,N,O) ligands"; *Dalton Transactions* 2012, 41:10136-10140.

International Search Report for International Patent Application No. PCT/2014/056495 mailed Apr. 29, 2014.

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(57) **ABSTRACT**

The present invention relates to a process for the preparation of a compound of formula (I), wherein X is —CH₂—, —CH₂—CH₂—, —CH₂—CH₂—CH₂— or —CH₂—CH₂—CH₂—CH₂—; Y₁ is —CH₂—; —CH₂—CH₂— or —NH—; Y₂ is NHR₇ or SH; wherein R₇ is hydrogen, C₁-C₄alkyl or phenyl; R₁ and R₂, independently from each other, represent aliphatic or aromatic groups; R₃ and R₄, independently from each other, represent aliphatic or aromatic groups; R₅ and R₆ are each hydrogen or represent together with the carbon atoms to which they are bonded, a phenyl ring; which process comprises reacting a compound of formula II [RuCl₂(R₈)_n]_m (II), wherein n is 1 and m is >1 which represents a polymeric structure if R₈ is a molecule containing two alkene or alkyne moieties coordinating in an haptic-2 coordination mode to the metal; or n is 4 and m is 1 if R₈ is a nitrogen, oxygen or sulfur containing molecule in which said nitrogen, oxygen or sulfur coordinate to the metal; in the presence of an inert solvent which boiling point is from 1 12° C. to 165° C. with a compound of formula (III), wherein R₅, R₆, Y₁ and Y₂ are as defined under formula I, and a phosphane of formula IV R₃R₄P—X—PR₁R₂ (iv), wherein R₁, R₂, R₃, R₄ and X are as defined under formula I.

8 Claims, No Drawings

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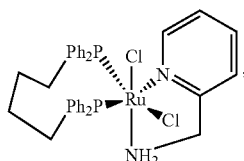
PROCESS FOR THE DIASTEREOSELECTIVE PREPARATION OF RUTHENIUM COMPLEXES

RELATED APPLICATION INFORMATION

This application is a 371 of International Application No. PCT/EP2014/056495, filed 1 Apr. 2014, which claims priority to EP Patent Application No. 13162679.8 filed 8 Apr. 2013, the contents of which are incorporated herein by reference herein.

The present invention relates to a process for the diastereoselective preparation of ruthenium complexes and their use as catalysts in the hydrogenation of C=N and C=O double bonds and in the oxidative synthesis of amides or esters.

It is known that the cis-form of certain ruthenium(II) complexes, for example $\text{RuCl}_2[\text{PPh}_2(\text{CH}_2)_4\text{PPh}_2][2-(\text{H}_2\text{NCH}_2)\text{C}_5\text{H}_4\text{N}]$ of formula Ia



are useful as a highly active hydrogenation catalysts. Said complex, its preparation and use as catalyst is described, for example, in WO 2005/105819 and in Crabtree et al. *Organometallics* 2011, 30, 4174-4179. The catalyst can either adopt a cis or a trans configuration with respect to the chloro ligands. The cis-form of this complex is especially preferred since it shows much higher reactivity in the above mentioned hydrogenation reactions (Baratta et al., *Organometallics* 2005, 24, 1660-1669). It is therefore highly desired to selectively prepare the cis-form of said complex.

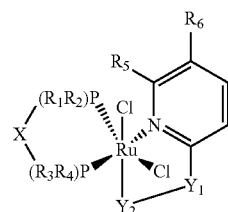
Clarke and co-workers report a procedure delivering structurally related complexes by consecutive addition of the ligands to the precursor $[\text{RuCl}_2(\text{Py})_2(\text{NBD})]$ in methyl-THF (Clarke et al. *Dalton Trans.* 2012, 41, 10136). However, the boiling point of methyl-THF is not sufficiently high to allow the formation of the highly active cis-complexes (the steric rearrangement needs high reaction temperatures e.g. boiling toluene). Another significant disadvantage of their procedure is the used catalyst precursor which is highly expensive and not available on an industrial scale. Further, the procedure reported by Clarke and co-workers includes the generation of two equivalents of toxic pyridine.

The synthesis of the compound of formula Ia according to WO 2005/105819, Crabtree et al. *Organometallics* 2011, 30, 4174-4179 and Baratta et al., *Organometallics* 2005, 24, 1660-1669 is based on a two step procedure. Further, long reaction times (20 hours) are described in preparatory examples 5 and 6 of WO 2005/105819. Moreover, all these procedures start from a catalyst precursor containing triphenylphosphine as ligand. Said catalyst precursor has the formula $\text{RuCl}_2(\text{PPh}_3)_n$ (with $n=3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9$ and 4.0) (Caulton et al., *J. Am. Chem. Soc.* 1975, 4221-4228). It can be derived from the formula of said catalyst precursor that it contains a large amount of triphenylphosphine ligand that has to be exchanged in the next step. From an economical and environmental point of view this exchange is highly problematic as at least three equivalents of phosphorous waste are generated per equivalent of catalyst.

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The aim of the present invention is therefore to provide a novel, robust process for the diastereoselective production of the cis-form of RuCl_2 complexes of formula I in high yields and good quality in an economically advantageous way.

Thus, according to the present invention, there is provided a process for the preparation of a compound of formula I



wherein

X is $-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ or $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$;

Y_1 is $-\text{CH}_2-$; $-\text{CH}_2-\text{CH}_2-$ or $-\text{NH}-$;

Y_2 is NHR_7 or SH ; wherein R_7 is hydrogen, C_1 - C_4 alkyl or phenyl;

R_1 and R_2 , independently from each other, represent aliphatic or aromatic groups;

R_3 and R_4 , independently from each other, represent aliphatic or aromatic groups;

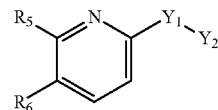
R_5 and R_6 are each hydrogen or together represent with the carbon atoms to which they are bonded, a phenyl ring; which process comprises reacting a compound of formula II



wherein n is 1 and m is >1 which represents a polymeric structure if R_8 is a molecule containing two alkene or alkyne moieties coordinating in an haptic-2 coordination mode to the metal;

or n is 4 and m is 1 if R_8 is a nitrogen, oxygen or sulfur containing molecule in which said nitrogen, oxygen or sulfur coordinate to the metal;

in the presence of an inert solvent which boiling point is from 112°C. to 165°C. with a compound of formula III



wherein R_5 , R_6 , Y_1 and Y_2 are as defined under formula I, and a phosphane of formula IV



wherein R_1 , R_2 , R_3 , R_4 and X are as defined under formula I.

In a preferred embodiment of the invention, X is preferably $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$.

In said preferred embodiment of the invention, R_8 is preferably cis,cis-cycloocta-1,5diene (cyclooctadiene or abbreviated as COD) or bicyclo[2.2.1]hepta-2,5-diene (norbornadiene or abbreviated as NBD) if n is 1 and $m > 1$; or is preferably dimethylsulfoxide resulting in $\text{RuCl}_2(\text{dmsO}-\kappa\text{O})(\text{dmsO}-\kappa\text{S})_3(\text{dmsO}-\kappa\text{O})$ or $\text{RuCl}_2(\text{dmsO}-\kappa\text{S})_4$ as precursors if n is 4 and m is 1, but in particular cis,cis-cycloocta-1,5diene or bicyclo[2.2.1]hepta-2,5-diene.

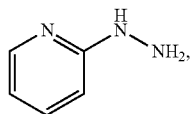
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In said preferred embodiment of the invention, R_1 , R_2 , R_3 and R_4 are preferably phenyl and R_5 and R_6 are preferably hydrogen or together represent with the carbon atoms to which they are bonded, a phenyl ring; Y_1 is preferably $-\text{CH}_2-$, and Y_2 is preferably NH_2 .

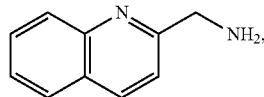
The boiling point of the inert solvent according to the process of the invention is given at an atmospheric pressure of 1023.25 hPa. To achieve economically favourable reaction times, the reaction is performed at temperatures above 112°C . (temperature at a pressure of 1023.25 hPa). Preferred inert solvents are ketones, preferably cyclohexanone, esters, preferably ethyl butyrate and aromatic solvents or mixtures of aromatic solvents with a boiling point from 112°C . to 165°C . (temperature at a pressure of 1023.25 hPa), preferably xylene and halogenated aromatic compounds preferably chlorobenzene.

In said preferred embodiment of the invention, the inert solvent is preferably cyclohexanone, ethyl butyrate, xylene or chlorobenzene.

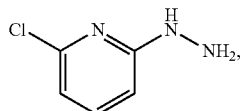
Preferred compounds of formula III for the process according to the invention are selected from the group consisting of the formulae



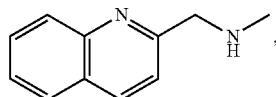
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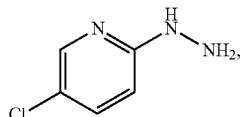
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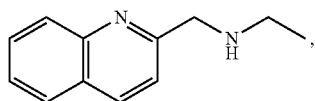
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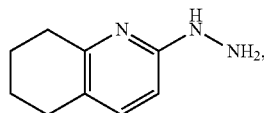
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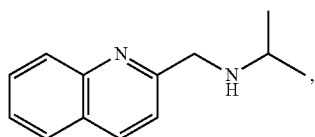
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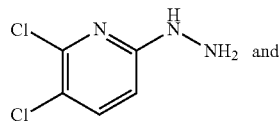
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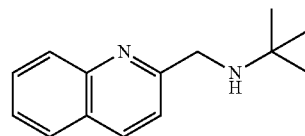
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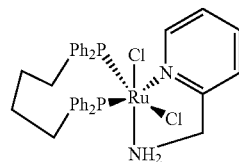
wherein the radicals signify methyl groups. The use of said preferred compounds of formula III-1 to III-10 are also especially preferred in said preferred embodiment of the invention mentioned above.

A preferred embodiment of the process according to the invention is characterized by reacting a compound of formula

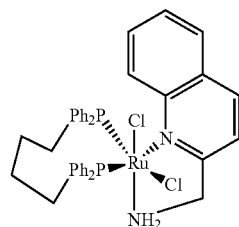


wherein (m is >1); with 1.225 equivalents of a bidentate amine ligand preferably 2-picolylamine or the compound (III-2) in presence of 1 equivalent of a bidentate phosphine ligand preferably 1,4-bis(diphenylphosphino)butane in an inert solvent like cyclohexanone at a reaction temperature from 125 to 135°C .

The process according to the present invention is especially useful for the preparation of catalysts of the formulae Ia and Ib



(Ia)



(Ib)

The catalyst of the formula Ib is novel and represent a further object of the invention. The catalyst of the formula Ib crystallize more rapidly during subsequent purification; thereby enabling faster filtration times and lower residual catalyst in the substrate solution. This is in particular of importance for the large scale production of the catalyst.

The process is preferably performed as an one pot procedure. An advantage of the one pot procedure in particular for large-scale manufacturing are significantly reduced reaction times. In addition, phosphane containing waste is remarkably reduced compared to the prior art process described in WO 2005/105819.

The synthesis of the precursors can be accomplished by a person skilled in the art following the procedures described in Albers et. al. *Inorg. Synth.* 1989, 26, 68-77 for $\text{RuCl}_2(\text{cyclooctanediene})$ and Albers et. al. *Inorg. Synth.* 1989, 26, 249-258 for $\text{RuCl}_2(\text{bicyclo}[2.2.1]\text{hepta-2,5-diene})$ or Castellano et. al. *Inorg. Chim. Acta.* 2009, 363, 283-287 for $[\text{RuCl}_2$

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(dmsO-κS)₃(dmsO-κO)] as well as Riant et. al. *Chem. Eur. J.* 2009, 15, 6267-6268) for RuCl₂(dmsO-κS)₄.

The catalyst precursors RuCl₂(cyclooctanediene) and RuCl₂(bicyclo[2.2.1]hepta-2,5-diene) show polymeric structures (illustrated by the definition m>1). In these cases the molecular formulae are more exactly represented by [RuCl₂(cyclooctanediene)]_m and [RuCl₂(bicyclo[2.2.1]hepta-2,5-diene)]_m, with m>1. This fact is also described in the above mentioned literature citations.

Preferably precursors with highest metal content and purities are used

typically 29-37 weight-% ruthenium for [RuCl₂(cyclooctanediene)]_m,

31-39 weight-% ruthenium for [RuCl₂(bicyclo[2.2.1]hepta-2,5-diene)]_m and

16-21 weight-% ruthenium for [RuCl₂(dmsO-κS)₃(dmsO-κO)] and for RuCl₂(dmsO-κS)₄.

The efficiency of the catalysts of formula Ia made from [RuCl₂(COD)]_m as the precursor is equivalent to that of the catalyst of formula Ia made from [RuCl₂(PPh₃)_n] as the precursor for both reduction under hydrogen atmosphere and transfer hydrogenation.

TABLE 1

| Catalytic reduction of acetophenone to 1-phenylethanol under hydrogen atmosphere in the presence of ruthenium complexes | | | | |
|---|---|-----------------|-----------------|-------------------------|
| Pre-catalyst | Molar ratio Acetophenone/ Ru/Base | Pressure bar | Conversion % | Reaction Time min |
| [RuCl ₂ (PPh ₃) _n] | 4000/1/85 | 9 | 99 | 225 |
| [RuCl ₂ (COD)] _m | 4000/1/85 | 9 | 99 | 225 |

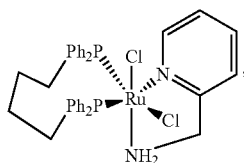
TABLE 2

| Catalytic reduction of acetophenone to 1-phenylethanol in the presence of ruthenium complexes | | | |
|---|---|-----------------|-------------------------|
| Pre-catalyst | Molar ratio Acetophenone/ Ru/Base | Conversion % | Reaction Time min |
| [RuCl ₂ (PPh ₃) _n] | 4000/1/85 | 98 | 30 |
| [RuCl ₂ (COD)] _m | 4000/1/85 | 94 | 60 |

PREPARATORY EXAMPLES

Example P1

Preparation of RuCl₂[PPh₂(CH₂)₄PPh₂][2-H₂NCH₂)C₉H₆N] of formula Ia



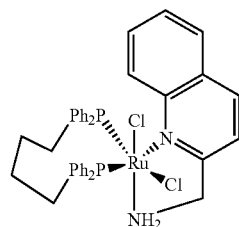
The catalyst precursor, preferably [RuCl₂(COD)]_m (1 eq.) (COD=cis,cis-cycloocta-1,5diene), 1,4-bis(diphenylphosphino)butane (1.0-1.2 eq., preferably 1.0 eq.) and 2-picoly-

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lamine (1.0-1.4 eq., preferably 1.225 eq.) were dissolved in one of the above mentioned solvents, preferably methyl isobutylketone (10-20 ml/g Ru-precursor, preferably 20 ml/g). The mixture was heated to reflux for 3-5 hours and then cooled to ambient temperature. The solid precipitate was filtered off and washed with the same solvent that was used for the reaction. A person skilled in the art can determine the cis-/trans-isomeric ratio by NMR. The diastereomeric ratios generated by this method are usually in the range of d.r. (diastereomeric ratio) >98% towards the cis isomer. The same results can be achieved starting with [RuCl₂(dmsO-κS)₃(dmsO-κO)], [RuCl₂(dmsO-κS)₄] or [RuCl₂(bicyclo[2.2.1]hepta-2,5-diene)]_m as precursor.

Example P2

Preparation of RuCl₂[PPh₂(CH₂)₄PPh₂][2-H₂NCH₂)C₉H₆N] of formula Ib

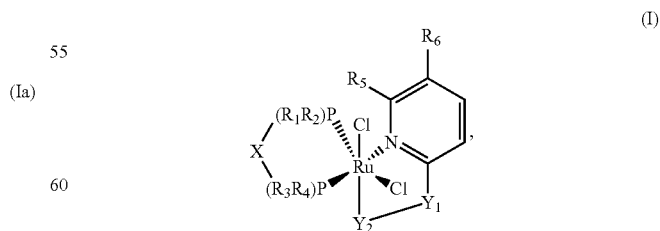


(Ib)

The catalyst precursor, preferably [RuCl₂(COD)]_m (1 eq.), 1,4-bis(diphenylphosphino)butane (1.0-1.2 eq., preferably 1.0 eq.) and 2-quinolylmethylamine (1.0-1.4 eq., preferably 1.225 eq.) were dissolved in one of the above mentioned solvents, preferably cyclohexanone (10-20 ml/g Ru-precursor, preferably 20 ml/g). The mixture was heated at 130° C. for 1 hour and then cooled to ambient temperature. The solid precipitate was filtered off and washed with the same solvent that was used for the reaction. A person skilled in the art can determine the cis-/trans-isomeric ratio by NMR. The diastereomeric ratios generated by this method are usually in the range of d.r. (diastereomeric ratio) >98% towards the cis isomer. The same results can be achieved starting with [RuCl₂(dmsO-κS)₃(dmsO-κO)], [RuCl₂(dmsO-κS)₄] or [RuCl₂(bicyclo[2.2.1]hepta-2,5-diene)]_m as precursor.

What is claimed is:

1. A process for the preparation of a compound of formula I



wherein

X is —CH₂—, —CH₂—CH₂—, —CH₂—CH₂—CH₂— or —CH₂—CH₂—CH₂—CH₂—;

Y₁ is —CH₂—; —CH₂—CH₂— or —NH—;

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Y_2 is NHR_7 or SH ; wherein R_7 is hydrogen, C_1 - C_4 alkyl or phenyl;

R_1 and R_2 , independently from each other, represent aliphatic or aromatic groups;

R_3 and R_4 , independently from each other, represent aliphatic or aromatic groups;

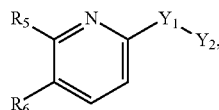
R_5 and R_6 are each hydrogen or together represent with the carbon atoms to which they are bonded, a phenyl ring; which process comprises reacting a compound of formula II



wherein n is 1 and m is >1 which represents a polymeric structure if R_8 is a molecule containing two alkene or alkyne moieties coordinating in an hapto-2 coordination mode to the metal;

or n is 4 and m is 1 if R_8 is a nitrogen, oxygen or sulfur containing molecule in which said nitrogen, oxygen or sulfur coordinate to the metal;

in the presence of an inert solvent which boiling point is from $112^\circ C.$ to $165^\circ C.$ with a compound of formula III



wherein R_5 , R_6 , Y_1 and Y_2 are as defined under formula I, and a phosphane of formula IV



wherein R_1 , R_2 , R_3 , R_4 and X are as defined under formula I.

2. A process according to claim 1 for the preparation of a compound of formula I, wherein

X is $-CH_2-CH_2-CH_2-CH_2-$.

3. A process according to claim 2 for the preparation of a compound of formula I, wherein

R_8 is cyclooctadiene or bicyclo[2.2.1]hepta-2,5-diene if n is 1 and $m >1$; or is dimethylsulfoxide if n is 4 and m is 1.

4. A process according to claim 2 for the preparation of a compound of formula I, wherein

R_1 , R_2 , R_3 and R_4 are phenyl and

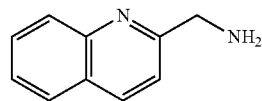
R_5 and R_6 are hydrogen or together represent with the carbon atoms to which they are bonded, a phenyl ring;

Y_1 is $-CH_2-$, and

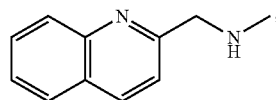
Y_2 is NH_2 .

5. A process according to claim 1, wherein the compound of formula III is represented by compounds from the group consisting of the formulae

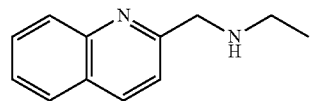
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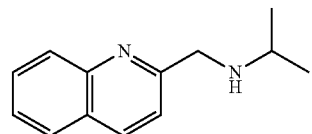
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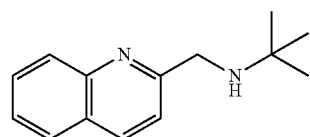
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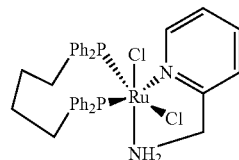
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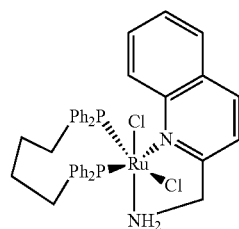
6. A process according to claim 1 performed as a one pot procedure.

7. A process according to claim 1 for the preparation of the compound of formula Ia



(Ia)

8. The compound of formula Ib



(Ib)

* * * * *